Abacavir (ABC, Ziagen)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Pediatric oral solution: 20 mg/mL

Tablets: 300 mg (scored)

Combination Tablets:

- *With lamivudine (3TC):* ABC 600 mg + 3TC 300 mg (Epzicom)
- *With zidovudine (ZDV) and 3TC:* ABC 300 mg + ZDV 300 mg + 3TC 150 mg (Trizivir)

Dosing Recommendations

Neonate/infant dose:
ABC is not approved for infants <3 months of age.

Pediatric dose:
Oral solution (>3 months of age):
8 mg/kg (maximum 300 mg) twice daily.

In clinically stable patients with undetectable viral load and stable CD4 cell count, may consider using once-daily ABC dosing: 16 mg/kg/dose to maximum of 600 mg once daily (see Pediatric Use).

Scored 300-mg tablet (body weight ≥14 kg):

Weight (kg)	Twice-Daily Dosage Regimen		
	AM Dose	**PM Dose**	**Total Daily Dose**
14–21 kg	½ tablet (150 mg)	½ tablet (150 mg)	300 mg
>21 to <30 kg	½ tablet (150 mg)	1 tablet (300 mg)	450 mg
≥30 kg	1 tablet (300 mg)	1 tablet (300 mg)	600 mg

Adolescent (≥16 years of age)/adult dose:
300 mg twice daily or 600 mg once daily.

Trizivir
Adolescent (body weight ≥40 kg)/adult dose:
One tablet twice daily.

Epzicom
Adolescent (≥16 years of age)/adult dose:
One tablet once daily.

Selected Adverse Events

- Hypersensitivity reaction (HSR) that may be fatal; symptoms may include fever; rash; nausea; vomiting; malaise or fatigue; loss of appetite; respiratory symptoms such as sore throat, cough, shortness of breath.
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of ABC; however, other studies have not substantiated this finding, and there are no data in children.

Special Instructions

- Test patients for the HLA-B*5701 allele before starting therapy to predict risk of hypersensitivity; patients with the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested.
- ABC can be given without regard to food.
- Caution patients and parents about the risk of serious, potentially fatal HSR. Do not rechallenge.

Metabolism

- Metabolized by alcohol dehydrogenase and glucuronyl transferase; renal excretion of metabolites 82%.
- ABC requires dosage adjustment in hepatic insufficiency. Do not use Trizivir and Epzicom (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (See also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#).)***:***

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P (CYP) 450 enzymes. Thus, it should not cause changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Abacavir is metabolized by alcohol dehydrogenase and glucuronyl transferase. Alcohol increases abacavir levels by 41%.

Major Toxicities:

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- *Less common (more severe):* Serious and sometimes fatal HSRs observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by rash or by signs or symptoms in two or more of the following groups: (1) fever; (2) constitutional, including malaise, fatigue, or achiness; (3) gastrointestinal (GI), including nausea, vomiting, diarrhea, or abdominal pain; or (4) respiratory, including dyspnea, cough, or pharnygitis. Laboratory and imaging abnormalities include elevated liver function tests (LFTs), elevated creatine phosphokinase (CPK), elevated creatinine, lymphopenia, and pulmonary infiltrates. This reaction generally occurs in the first 6 weeks of therapy and has occurred after a single dose. If an HSR is suspected, abacavir should be stopped and not restarted because hypotension and death have occurred upon rechallenge. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis may occur.
- *Rare:* Increased liver enzymes, elevated blood glucose, elevated triglycerides (TGs), and possible increased risk of myocardial infarction (in observational studies in adults).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ABC.html).

Pediatric Use: Abacavir is Food and Drug Administration (FDA) approved for use in children with HIV infection as one of the drugs for part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral (ARV) therapy. The liquid formulation of abacavir is more palatable than zidovudine; it has less of an effect on mitochondrial function than zidovudine, stavudine, or didanosine; and it has more durable antiviral effectiveness in pediatric trials[1-2]. The risk of abacavir hypersensitivity syndrome, the major toxicity limiting abacavir's use, is greatly reduced by testing patients for HLA-B*5701 and by not using abacavir in those who test positive for the HLA-B*5701 allele.

Pharmacokinetic (PK) studies of abacavir in children <12 years of age have demonstrated that children have more rapid clearance of abacavir than adults and that pediatric doses approximately twice the directly scaled adult dose are necessary to achieve similar systemic exposure[3-4]. Metabolic clearance of abacavir in adolescents and young adults (ages 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults[5].

Plasma area under the drug concentration by time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak[6-7]. Intracellular concentrations of NRTIs are most strongly associated with antiviral effectiveness, and the active form of abacavir is the intracellular metabolite carbovir triphosphate[8-9]. Measurement of intracellular carbovir triphosphate is more difficult than measurement of

plasma AUC, so the abacavir plasma AUC is often taken as a proxy measurement for intracellular concentrations. However, this relationship is not sufficiently strong that changes in plasma AUC can be assumed to reflect true changes in intracellular active drug. For example, although overall intracellular carbovir triphosphate was correlated with abacavir plasma AUC , this relationship was not found when gender was considered in PK modeling[10] because carbovir triphosphate concentrations were higher in females than in males[10-12]. This effect of gender on intracellular triphosphates has also been found with zidovudine and lamivudine[8, 13].

In studies in adults, abacavir plasma AUC is decreased 17% by concurrent use of atazanavir/ritonavir and decreased 32% by concurrent use of lopinavir/ritonavir[14]. In a study comparing PK parameters of abacavir in combination with either lopinavir/ritonavir or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of lopinavir/ritonavir, but the carbovir triphosphate concentration seemed to increase in the lopinavir/ritonavir group[12].

These effects of gender and concurrent PI use add to the complexity of linking readily available plasma abacavir AUC with more difficult to obtain but pharmacodynamically more important intracellular carbovir triphosphate concentrations. These effects also need to be kept in mind when considering data supporting the use of once-daily abacavir in children (presented in the table below).

Abacavir 600 mg once daily is standard for use in adults, but once-daily use for children is still controversial. The PENTA-13 crossover trial studied abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in 24 children ages 2–13 years who had undetectable or low, stable viral loads at the time of changing from twice-daily to once-daily abacavir. This study showed equivalent AUC_{0-24} for both drugs and improved acceptability in the once-daily dosing arm[15-16]. However, trough concentrations were lower in younger children (ages 2–6 years) receiving the once-daily regimen[16]. The PENTA-15 crossover trial studied 18 children ages 3–36 months, again comparing abacavir 16 mg/kg once daily versus 8 mg/kg twice daily in children with viral loads <400 copies/mL or "stable" on twice-daily abacavir at baseline. AUC_{0-24} and clearance were similar on the once- and twice-daily regimens. After the change from twice-daily to once-daily abacavir, viral load remained <400 copies/mL in 16 of 18 participants through 48 weeks of monitoring[17]. A study of 41 children ages 3–6 years (median age 7.6 years) in Uganda who were stable on twice-daily abacavir also showed equivalent AUC_{0-24} and good clinical outcome (disease stage and CD4 cell count) after the switch to once-daily abacavir, with median follow-up of 1.15 years. Viral load testing was not done[18].

Abacavir Steady State Pharmacokinetics When Dosed Once Daily or Twice Daily*

Study/(reference)	PENTA 15[17]		PENTA 13[16]		Arrow[18]		(5)		(10)	
Location	Europe		Europe		Uganda		US		US	
N	18		14		36		15	15	27	
Age (years)	2		5		7		16[a]	22[a]	45[a]	
Sex (% male)	56%		43%		42%		53%	53%	70%	
Race (% black or African American)	78%				100%		53%	60%	18%	
Body weight (kg)	11		19		19		63[a]	72[a]	NA	
Concurrent PI use	8		1		0		9	0	NA	
Dosing Interval (hours)	12	24	12	24	12	24	12	12	12	24
Administered dose median (mg/kg) or fixed amount (mg)	8.04	16.02	8.1	16.4	19.6[c]	19.1	300[d]	300[d]	300[d]	600[d]
Administered dose range (mg/kg)	7.7–8.3[e]	15.5–16.3[e]	5.0–8.4	15.6–17.1	15.4–23.1[c]	14.6–23.1				
AUC_{0-24} (mg*hr/L)	10.85[b]	11.57[b]	9.91[b]	13.37[b]	15.6[b]	15.28[b]	7.01	6.59	7.90[b]	8.52[b]
C_{max} (mg/L)	1.38[b]	4.68[b]	2.14[b]	4.80[b]	4.18[b]	6.84[b]	2.58	2.74	1.84[b]	3.85[b]
C_{min} (mg/L)	0.03[b]	<0.015[b]	0.025[b]	<0.015[b]	0.021[b]	0.006[b]				
Cl/F/kg (L/hr/kg)	1.47[b]	1.38[b]	1.58[b]	1.16[b]	1.23[b]	1.24[b]	9.80[f]	12.10[f]		
Carbovir-triphosphate AUC_{0-24} (h*fmol/10^6 cells)							530[g]	315[g]	814	1,051

* Data are medians except as noted
[a.] mean
[b.] geometric mean
[c.] total daily dose in mg/kg (divided doses were given but sometimes in unequal amounts morning and evening)
[d.] total dose in mg
[e.] interquartile range
[f.] clearance in ml/min/kg
[g.] AUC in fmol/10^6 cells

No clinical trials exist involving children who initiated combination antiretroviral therapy (cART) with once-daily dosing of abacavir. All three pediatric studies described in the table above enrolled only patients who had low viral loads or were "clinically stable" on twice-daily abacavir before changing to once-daily dosing. Therefore, the Panel suggests that in clinically stable patients with undetectable viral loads and stable CD4 cell counts, switching to once-daily dosing of abacavir (at a dose of 16 to 20 mg/kg/dose to maximum of 600 mg once daily) could be considered.

References

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